Remarks

Applicants thank the Examiner for the indication of allowable subject matter in claims 1 – 26.

Claims 27 and 29 were rejected under 35 USC §112, second paragraph as being indefinite. Claim 27 has been amended so that claim 27 is now dependent from claim 26, which recites a pharmaceutical composition. Applicants respectfully submit that claims 27 and 29 are now in condition for allowance.

Claims 28 and 29 were rejected under 35 USC §112, first paragraph. The Office Action suggests that the specification does not support the claimed subject matter. Applicants respectfully traverse this rejection. With regard to the claimed treatment of pain, the Formalin test in mice described in paragraphs [0039] to [0044] of the specification as filed demonstrates the effectiveness of the claimed compounds.

The specification also demonstrates that the claimed compounds show an affinity for the NMDA-receptor channel, as shown in the receptor binding studies found at paragraphs [0030] to [0038] of the specification as filed. It is generally accepted among those skilled in the art that the NMDA-receptor channel is a suitable target for treating the various disorders claimed in claims 28 and 29. As evidence of this, attached to this response are drug abstract listings from several issues of the Drug Data Report published by Prous Science of Barcelona, Spain. For example, compound 225249 is described as a noncompetitive antagonist at the glycine site of the NMDA receptor. The abstract for compound 225249 states that the compound is "potentially useful for the treatment and prophylaxis of cerebral ischemic/anoxic disorders, and for the treatment of neurodegenerative

disorders such as Parkinsonism and Alzheimer's disease, as well as epilepsy, schizophrenia and migraine." Thus, compound 225249 is described as having the capability to treat a wide variety of conditions based on its affinity for the NMDA receptor. In another example, compound 315794 is described as a glutamate antagonist with activity against sites that include the glycine site of NMDA receptors. Compound 315794 is described as "Potentially useful for the treatment of cerebral ischemia, chronic neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and Huntington's disease, seizure disorders, schizophrenia, anxiety, pain and drug abuse."

As seen in the drug abstracts, those of skill in the art recognize that compounds with an affinity for the NMDA-receptor channel have beneficial treatment properties against a wide range of conditions, not just a single condition. Additionally, the 6 highlighted compounds show activity at the NMDA-receptor and each of the compounds treats a plurality of the conditions recited in the claims. As a result, those of skill in the art would recognize that the claimed compounds would be effective for treatment of the conditions recited in the claims based on the affinity of the claimed compounds for the NMDA-receptor channel. Thus, Applicants respectfully request allowance of claims 28 and 29.

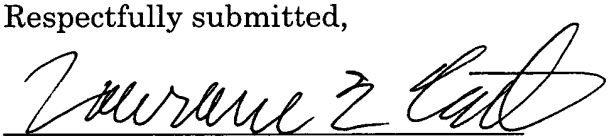
In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #148/50871).

Respectfully submitted,

July 8, 2003



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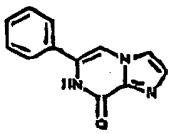
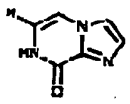
225249

6-Phenylimidazo[1,2-*a*]pyrazin-8(7*H*)-one



C12-H9-N3-O ; Mol wt: 211.22

ACTION – Noncompetitive antagonist at the glycine site of the NMDA receptor, potentially useful for the treatment and prophylaxis of cerebral ischemic/anoxic disorders, and for the treatment of neurodegenerative disorders such as parkinsonism and Alzheimer's disease, as well as epilepsy, schizophrenia and migraine. Other exemplified imidazopyrazinones include the following:



227609; C12-H8-Cl-N3-O: R= 4-Cl-Ph
227610; C12-H7-Cl2-N3-O: R= 3,4-(Cl)2-Ph
227611; C11-H10-N4-O: R= 2-Pyr
227612; C10-H7-N3-O2: R= 2-furyl

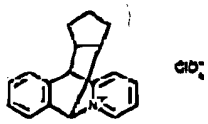
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. Albup, J.-C., et al. (Rhone-Poulenc Rorer SA) *7H-Imidazo[1,2-a]pyrazin-8-one NMDA receptor antagonists*. WO 9513534.

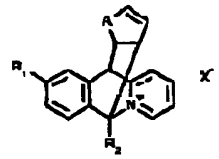
226635

11,12,13,14,15,16-Hexahydro-6*H*-6,11[1',2']cyclopentabenzo[*b*]quinolizinium perchlorate



C16-H16-Cl-N-O4 ; Mol wt: 347.80

ACTION – Neuroprotective agent that binds to the phencyclidine (PCP) receptor (K_i = 366 nM against binding of [^{3}H]-TCP in rat brain preparations), and thus acts as a noncompetitive antagonist of the NMDA receptor. Compound antagonized NMDA-induced neurotoxicity in cultured fetal mouse cortical neurons (IC_{50} = 8400 nM). A compound within a series of 6,11-substituted-6,11-dihydrobenzo-[*b*]quinolizinium salts, wherein the following are also included:



228143; C19-H19-Br-N: R1=R2= H, A= CH2CH2, X= Br
228144; C18-H15-Br-N: R1= Br, R2= H, A= CH2, X= Br
228145; C10-H13-CHF-N-O4: R1= F, R2= H, A= CH2, X= ClO4
228146; C19-H18-Cl-N-O4: R1= H, R2= Me, A= CH2, X= ClO4
228147; C21-H21-Cl-N-O4: R1=R2= H, A= C(Me)2=C, X= ClO4
228148; C18-H16-Br-N: R1=R2= H, A= CH2, X= Br

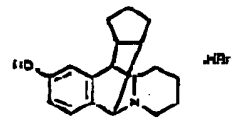
SOURCE – Sterling Winthrop.

REFERENCES

1. DeHaven-Hudkins, D.L. and Malone, J.R. (Sterling Winthrop, Inc.) *6,11-Substd.-6,11-dihydrobenzo[b]quinolizinium salts and compns. and method of use thereof*. US 5430039.

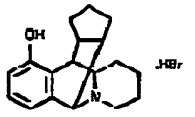
226654

9-Hydroxy-1,2,3,4,6,11,11a,12,13,14,15,16-dodecahydro-6,11[1',2']cyclopentabenzo[*b*]quinolizine hydrobromide



C18-H23-N-O HBr ; Mol wt: 350.30

ACTION – Neuroprotective agent that potently binds to the phencyclidine (PCP) receptor (K_i = 2.31 nM against [^{3}H]-TCP binding in rat brain preparations), and thus acts as a noncompetitive antagonist of the NMDA receptor. Compound showed an IC_{50} of 42 nM for inhibition of NMDA-induced neurotoxicity in cultured fetal mouse brain neurons. Another specifically claimed 6,11-cyclyl-1,2,3,4,5,6,11,11a-octahydrobenzo[*b*]quinolizine is:

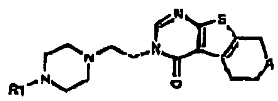


228142; C18-H25-N-O.HBr

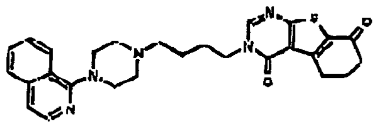
SOURCE – Sterling Winthrop.

REFERENCES

1. DeHaven-Hudkins, D.L., et al. (Sterling Winthrop, Inc.) *6,11 Cyclyl-1,2,3,4,5,6,11,11a-octahydrobenzo[b]quinolizine and compns. and method of use thereof*. US 5430139.



Compound	R1	A	Formula
315731	1-Isoquinolyl	-O-	[illegible]
315732	1-Isoquinolyl	-S(O)	[illegible]
315733	1-Isoquinolyl	-N(SO2Me)	[illegible]
315735	8-quinolyl	S	[illegible]
315738	8-quinolyl	S(O)	[illegible]
315740	8-quinolyl	N(SO2Me)-	[illegible]



315730: C27 H29 N5 O2 S

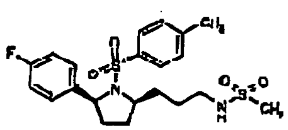
SOURCE – Abbott.

REFERENCES

1. Steiner, G. et al. (Knoll AG) *Pyrimidine derivs. and their use for preventing and treating cerebral ischaemia.* DE 10031390, WO 0102568.

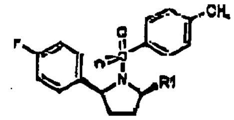
315763

N-[3-[(2*R**,5*R**)-5-(4-Fluorophenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-2-yl]propyl]methanesulfonamide

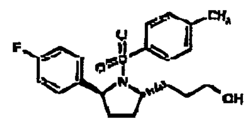


C21 H27 F N2 O4 S2; Mol wt: 454.5843

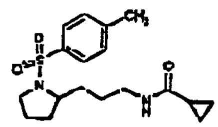
ACTION – A group I metabotropic glutamate receptor (mGlu) agonist with an EC_{50} of 0.16 µM at rat $mglu_{1a}$ receptors expressed in EBNA cells. Potentially useful for the treatment of restricted brain function associated with bypass operations or poor blood supply, spinal cord and head trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy, cognitive disorders, memory deficits, pain, schizophrenia, parkinsonism and conditions which lead to glutamate deficiency functions such as muscle spasms, convulsions, migraine, urinary incontinence, nicotine and opiate addiction, psychosis, anxiety, vomiting, dyskinesia and depression. Other exemplified sulfonylpyrrolidine derivatives are:



Compound	R1	Isomer	Formula
315764	CN	2R*,5S*	[illegible]
315765	CH2Cl	2R*,5S*	[illegible]
315766	Cyclopropyl-CONHCH2	2R*,5R*	[illegible]
315770	5-Me-1,2,4-oxadiazol-3-yl-CH2	2R*,5S*	[illegible]
315776	2-Me-5-tetrazolyl-CH2	2R*,5S*	[illegible]
315779	2-tetrazolyl-CH2CH2	2R*,5S*	[illegible]
315780	1-imidazolyl-(CH2)3	2S,5S	[illegible]
315781	4,6-(Me)2-2-pyrimidinyl-(CH2)3	2R*,5R*	[illegible]
315782	1,3,4-oxadiazol-2-yl	2R*,5S*	[illegible]
315783	2-oxazolyl-(CH2)4	2R*,5R*	[illegible]



315777: C20 H24 F N O3 S



315778: C18 H26 N2 O3 S

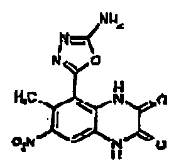
SOURCE – Roche.

REFERENCES

1. Mutel, V. and Wichmann, J. (F. Hoffmann-La Roche AG) *Sulfonylpyrrolidine derivs. useful for the treatment of neurological disorders.* WO 0202554.

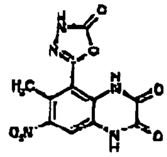
315794

5-(5-Amino-1,3,4-oxadiazol-2-yl)-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoxaline-2,3-dione



C11 H8 N6 O5; Mol wt: 304.2212

ACTION – Glutamate antagonist with *in vitro* activity against AMPA receptors and the glycine site of NMDA receptors. Potentially useful for the treatment of cerebral ischemia, chronic neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and Huntington's disease, seizure disorders, schizophrenia, anxiety, pain and drug abuse. Another exemplified quinoxaline-2,3-dione derivative is:



315735: C11 H7 N5 O6

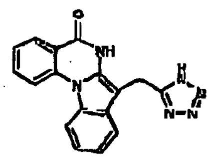
SOURCE – Pfizer.

REFERENCES

1. Kornberg, B.E. et al. (Pfizer Inc.) *Conformationally semi-constrained quinoxaline 2,3-diones as neuroprotective agents.* US 6340758.

316105

7-(1H-Tetrazol-5-ylmethyl)indolo[1,2-a]quinazolin-5(6H)-one



C17 H12 N6 O; Mol wt: 316.3228

ACTION – A specifically claimed compound from a group of indolo[1,2-a]quinazolin-5-one derivatives effective as a poly(ADP-ribose) polymerase (PARP, NAD+ ADP ribosyltransferase) inhibitors. Potentially useful for the treatment of a broad range of conditions including apoptosis, neural tissue damage resulting from ischemia–reperfusion injury, neurological and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, etc., vascular stroke, cardiovascular disorders including myocardial infarction and unstable angina, age-related macular degeneration, AIDS, arthritis, atherosclerosis, cachexia, cancer, diabetes, head and spinal cord trauma, immune senescence, inflammatory bowel disorders, osteoporosis, pain, renal failure, retinal ischemia, septic shock and skin aging.

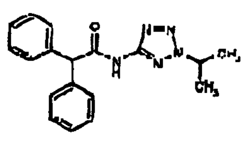
SOURCE – Novartis.

REFERENCES

1. Zimmermann, K. et al. (Novartis AG; Novartis-Erfindungen VmbH) *Indoloquinazolinones.* WO 0202284.

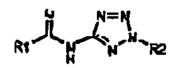
316188

N-(2-Isopropyl-2H-tetrazol-5-yl)-2,2-diphenylacetamide



C18 H19 N5 O; Mol wt: 321.3821

ACTION – Metabotropic glutamate receptor agonist giving an EC_{50} of 0.100 µM using rat $mGlu_{1a}$ receptors expressed in EBNA cells. Potentially useful for the treatment of acute and chronic neurological disorders such as restricted brain function caused by bypass operations or transplant, poor blood supply to the brain, head and spinal cord trauma, hypoxia caused by pregnancy, cardiac arrest, hypoglycemia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS dementia, eye injuries, retinopathy, cognitive disorders, memory deficits, schizophrenia and idiopathic or medicament-related parkinsonism. Other exemplified tetrazole derivatives are:



Compound	R1	R2	Formula
316192	CH(Ph)2	Me	$C_{16}H_{15}N_5O$
316193	9H-xanthen-9-yl	Me	$C_{16}H_{13}N_5O_2$
316196	9H-xanthen-9-yl	i-Pr	$C_{18}H_{17}N_5O_2$
316197	CH(Ph)2	CH2CF3	$C_{17}H_{14}F_3N_5O$
316198	9H-xanthen-9-yl	CH2CF3	$C_{17}H_{12}F_3N_5O_2$
316199	6,11-dihydrodibenzo[b,e]oxepin-11-yl	Et	$C_{18}H_{17}N_5O_2$
316200	9-thioxanthenyl	Et	$C_{17}H_{15}N_5OS$
316202	2-MeO-9-xanthenyl	Et	$C_{18}H_{17}N_5O_3$

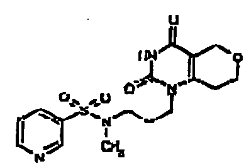
SOURCE – Roche.

REFERENCES

1. Adam, G. et al. (F. Hoffmann-La Roche AG) *Tetrazole derivs.* WO 0206254.

316201

N-[3-(2,4-Dioxo-2,3,4,5,7,8-hexahydro-1H-thiopyrano[4,3-d]pyrimidin-1-yl)propyl]-N-methylpyridine-3-sulfonamide



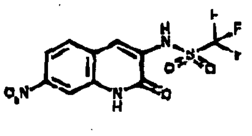
C16 H20 N4 O4 S2; Mol wt: 396.4900

ACTION – A poly(ADP-ribose)polymerase (PARP, NAD+ ADP-ribosyltransferase) inhibitor that displayed an IC_{50} of 0.04 µM against PARP, and was shown to protect endothelial cells from H_2O_2-induced toxicity with an IC_{50} of 0.25 µM. Potentially useful for the treatment of ischemia–reperfusion injury. Other exemplified uracil derivatives are:

NEURONAL INJURY INHIBITORS

198910

7-Nitro-3-(trifluoromethylsulfonamido)quinolin-2(1*H*)-one



C10-H6-F3-N3-O5-S ; Mol wt: 337.23

ACTION - Neuronal injury inhibitor with a dual mechanism of action; it antagonizes both AMPA/kainate and NMDA/glycine receptors, with K_i values lower than 1 mcM and a ratio of K_i AMPA/K_i NMDA of 0.60 in Xenopus oocyte preparations. A specifically claimed compound within a series of 3-sulfonylamino-2(1*H*)-quinolinone derivatives.

SOURCE - ADIR.

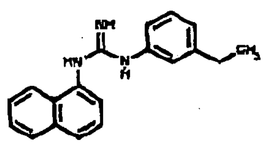
REFERENCES

1. Cordi, A. et al. (ADIR et Cie.) *3-Sulfonylamino-2(1H)-quinolinones and 7-aza derivs. as excitatory amino acids antagonists.* EP 542609, FR 2683818.

CNS-1086

199617

N[1]-(3-Ethylphenyl) *N*[3]-(1-naphthyl)guanidine



C19-H19-N3 ; Mol wt: 289.38

ACTION - Potential neuroprotective agent related to CNS-1102[1], NMDA receptor antagonist that acts as an ion channel blocker, as demonstrated in binding studies using [^{3}H]-MK-801 (IC_{50} = 38.6 nM).

SOURCE - Cambridge NeuroScience.

REFERENCES

1. Goldin, S.M. et al. (Cambridge NeuroScience, Inc.) *Subst. guanidines and derivs. thereof as modulators of neurotransmitter release and novel methodology for identifying neurotransmitter release blockers.* WO 9212[illegible].

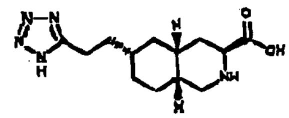
2. Hu, L.-Y. et al. *Synthesis and structure-activity studies of N-(1-naphthyl)-N'-(3-ethylphenyl)-N'-methylguanidine analogs (CNS 1102 analogs) for NMDA-ion-channel blockers.* 206th ACS Natl Meet (Aug 22-27, Chicago) 1993, Abst MEDI 154.

[1]Annu Drug Data Rep 1991, 13(11): 930.

LY-215490

199333

(±)-(3*S**,4a*R**,6*R**,8a*R**)-6-[2-(1*H*-Tetrazol-5-yl)-ethyl]decahydroisoquinoline-3-carboxylic acid



C13-H21-N5-O2 : Mol wt: 279.34

ACTION - Potent, competitive, selective and systemically active AMPA receptor antagonist, that showed an IC_{50} of 4.81 ± 1.23 mcM for displacement of [^{3}H]-AMPA binding in rat cortical slices, compared to respective values of 26.4 ± 1.9 and 247 ± 8 mcM for displacement of [^{3}H]-CGS-19755 (NMDA receptors) and [^{3}H]-kainic acid binding, with no affinity for glycine receptors. Compound antagonized AMPA-induced depolarizations in rat cortical slices with an IC_{50} of 6.0 ± 1.0 mcM and a pA_2 of 6.37 ± 0.02, being 5- to 10-fold less potent against kainic acid- and NMDA-induced depolarizations. In *in vivo* assays, it induced dose-dependent inhibition of AMPA-induced rigidity in mice (ED_{50} = 3.6 mg/kg i.p. 30 min before testing) and blocked maximal electroshock seizures in mice (ED_{50} = 9.0 mg/kg i.p. 30 min before testing), with no effect on NMDA-induced lethality and disruption in the horizontal screen assay at higher doses (ED_{50} = 19.6 mg/kg i.p. 30 min before testing), indicating a good separation between therapeutic doses and those producing side effects.

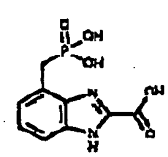
SOURCE - Lilly.

REFERENCES

1. Ornstein, P.L. et al. *(3SR,4aRS,6RS,8aRS)-6-[2-(1H-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid: A structurally novel, systemically active, competitive AMPA receptor antagonist.* J Med Chem 1993, 36(14): 2046.

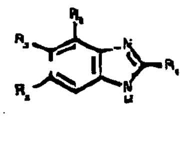
198295

4-(Phosphonomethyl)-1*H*-benzimidazole-2-carboxylic acid



C9-H9-N2-O5-P ; Mol wt: 256.15

ACTION - Agent for the treatment of neurotoxic injury associated with anoxia or ischemia following stroke, cardiac arrest or perinatal asphyxia; an NMDA receptor antagonist with a K_i = 1.8 mcM in the [^{3}H]-glutamate binding assay, whereas K_i was > 100 mcM when using [^{3}H]-kainate as the ligand. Significant *in vivo* antiischemic activity was demonstrated in a gerbil forebrain ischemia assay when given intraperitoneally at doses of 300 and 500 mg/kg, 30 min prior to carotid occlusion. Compound also exhibited anticonvulsant activity, as demonstrated by inhibiting electroconvulsive shock in mice and by protecting against motor function impairment at a dose of 56 mg/kg s.c. A representative compound from a wide series of specifically claimed diacid-containing benzimidazole derivatives, wherein the following are included:



200776: C10-H8-N10; R1 = 5-tetrazolyl, R2 = 5-tetrazolyl-CH2, R3 = R4 = H
200777: C11-H10-N10; R1 = 5-tetrazolyl, R2 = 5-tetrazolyl-CH2, R3 = Me, R4 = H
200778: C11-H9-Cl-N10; R1 = 5-tetrazolyl, R2 = 5-tetrazolyl-CH2CH2, R3 = H, R4 = Cl
200779: C9-H6-N10; R1 = R2 = 5-tetrazolyl, R3 = R4 = H
200780: C9-H11-N8-O-P; R1 = 5-tetrazolyl, R2 = CH2PO(NH2)2, R3 = R4 = H
200781: C10-H13-N8-O-P; R1 = 5-tetrazolyl, R2 = CH2PO(NH2)2, R3 = Me, R4 = H
200782: C10-H12-Cl-N8-O-P; R1 = 5-tetrazolyl, R2 = (CH2)2PO(NH2)2, R3 = H, R4 = Cl
200783: C10-H13-N8-O-P; R1 = 5-tetrazolyl, R2 = (CH2)2PO(NH2)2, R3 = R4 = H
200784: C11-H15-N8-O-P; R1 = 5-tetrazolyl, R2 = (CH2)3PO(NH2)2, R3 = R4 = H
200785: C11-H10-N2-O4; R1 = CO2H, R2 = CH2CO2H, R3 = Me, R4 = H
200786: C11-H10-N2-O4; R1 = CO2H, R2 = (CH2)2CO2H, R3 = R4 = H
200787: C12-H11-Cl-N2-O4; R1 = CO2H, R2 = (CH2)3CO2H, R3 = H, R4 = Cl
200788: C9-H6-N2-O4; R1 = R2 = CO2H, R3 = R4 = H
200789: C10-H8-N2-O4; R1 = R2 = CO2H, R3 = Me, R4 = H

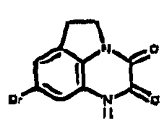
SOURCE - Searle.

REFERENCES

1 Vazquez M.L. (G.D. Searle & Co) *Diacid-containing benzimidazole compds. for treatment of neurotoxic injury.* US 5216003

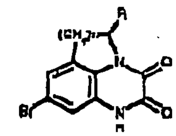
197041

8-Bromo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-2,3-dione



C10-H7-Br-N2-O2 ; Mol wt: 267.08

ACTION - Agent for the prevention and treatment of neurodegenerative disorders, a selective antagonist of glutamate receptors which strongly inhibits both [^{3}H]-MK-801 binding and [^{3}H]-glycine binding to the rat brain synaptic membrane preparation. Also claimed for its use as analgesic, antidepressant, anxiolytic or antipsychotic agent. A compound within a wide series of exemplified tricyclic quinoxalinedione derivatives, wherein the following are included:



200083: C11-H7-Br-N2-O4; R = CO2H, n = 1
200084: C18-H14-Br-N3-O3; R = CONHCH2Ph, n = 1
200085: C19-H16-Br-N3-O3; R = CONHCH2CH2Ph, n = 1
200086: C11-H10-Br-N3-O2; R = CH2NH2, n = 1
200087: C13-H11-Br-N2-O4; R = CH2CO2Me, n = 1
200088: C12-H9-Br-N2-O4; R = CH2CO2H, n = 1
200089: C19-H16-Br-N3-O3; R = CH2CONHCH2Ph, n = 1
200090: C17-H13-Br-N4-O3; R = NHCONHPh, n = 1
200091: C13-H11-Br-N2-O4; R = CO2Me, n = 2
200092: C12-H9-Br-N2-O4; R = CO2H, n = 2
200093: C19-H16-Br-N3-O3; R = CONHCH2Ph, n = 2
200094: C20-H18-Br-N3-O3; R = CONHCH2CH2Ph, n = 2
200095: C14-H13-Br-N2-O4; R = CH2CO2Me, n = 2
200096: C12-H10-Br-N3-O3; R = CONH2, n = 2
200097: C12-H12-Br-N3-O2; R = CH2NH2, n = 2

SOURCE - Sumitomo.

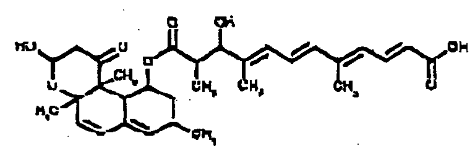
REFERENCES

1 Nagata R. et al. (Sumitomo Pharm. Co. Ltd.) *Tricyclic [illegible] antagonists.* JP 09117276, WO 9204100

NG-111

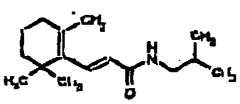
196611

3-Hydroxy-2,4,8-trimethyldodeca-4,6,8,10-tetraenedioic acid 1-(3-hydroxy-4a,8,10b-trimethyl-2,3,4a,5,9,10,10a,10b-octahydro-1*H*-naphtho[2,1-*b*]pyran-10-yl) monoester



C31-H40 O8 ; Mol wt: 540.65

ACTION - Cerebroprotective agent isolated from *Aspergillus versicolor* F5015, which promotes the production of nerve growth factor (NGF) by 225% at 0.03 mcg/ml in mouse fibroblasts. Potentially useful for the treatment of dementia. Another specifically claimed decalin derivative is:



268481: C18 H27 N O

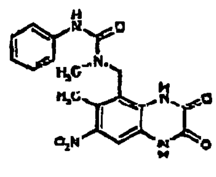
SOURCE Shionogi.

REFERENCES

1. Kanemasa, T. et al. (Shionogi & Co. Ltd.) *[illegible] Type calcium channel antagonist.* WO 9841121.

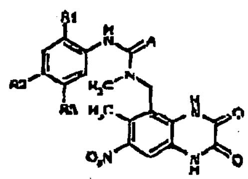
266182

N-Methyl-*N*-(6-methyl-7-nitro-2,3 dioxo 1,2,3,4 tetrahydroquinoxalin-5-ylmethyl)-*N'*-phenylurea



C18 H17 N5 O5; Mol wt: 383.3623

ACTION – Glutamate receptor antagonist acting at AMPA, kainate and, particularly, the glycine binding site of NMDA receptors (IC_{50} = 0.13, 0.82 and 0.008 μM, respectively). Claimed for the treatment of stroke, cerebral hypoxia/ischemia, Alzheimer's disease, Parkinson's disease and Huntington's disease. Within this series of substituted quinoxaline-2,3-diones, the following are also included:



Compound	R1	R2	R3	A	Formula
266914	H	OMe	H	O	[illegible]
266915	H	OMe	H	S	[illegible]
266917	Me	Me	H	O	[illegible]
266918	OMe	H	OMe	O	[illegible]
266919	CF3	H	H	O	[illegible]
266920	H	CO2Et	H	O	[illegible]

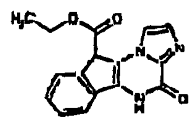
SOURCE – Warner-Lambert.

REFERENCES

1. Nikam, S.S. (Warner-Lambert Co.) *Urea and thiourea derivs. of substd. quinoxaline 2,3-diones as glutamate receptor antagonists.* WO 9823599.

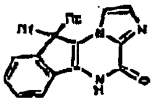
268738

4-Oxo-5,10-dihydro-4*H*-imidazo[1,2-*a*]indeno[1,2-*e*]pyrazine-10-carboxylic acid ethyl ester



C16 H13 N3 O3; Mol wt: 295.2967

ACTION – Cerebral antiischemic and neuroprotective agent, an AMPA receptor antagonist that also acts as a noncompetitive glycine-site NMDA receptor antagonist. Within this series of specifically claimed imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one derivatives, the following are also included:



Compound	R1	R2	Formula
268738	CO2Et	H	[illegible]
268739	1-Me-2-imidazolyl CH2	H	[illegible]
268740	(R) NHCOC(OMe)(Ph)CF3	H	[illegible]
268741	NH2	Me	[illegible]
268742	[illegible]		[illegible]
268743	CH2CH2CO2H	NH2	[illegible]
268744	1-Me-5-imidazolyl-CH2	H	[illegible]
268745	[illegible]	H	[illegible]
268746	NH2	Bu	[illegible]

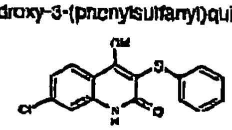
SOURCE – Rhône-Poulenc Rorer.

REFERENCES

1. [illegible], J.-C. et al. (Rhône-Poulenc Rorer SA) *Imidazo [1,2-a]-indeno [1,2-e] pyrazin-4-one derivs. and pharmaceutical compsns. containing them.* US [illegible] WO [illegible]

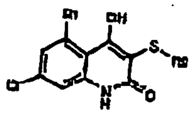
269005

7-Chloro-4-hydroxy-3-(phenylsulfanyl)quinolin-2(1*H*)-one



C15 H10 Cl N O2 S; Mol wt: 303.7650

ACTION – Potent and specific antagonist at the strychnine-insensitive glycine binding site on the NMDA receptor complex, reported to possess good CNS penetration and high solubility. Claimed for the treatment or prevention of ischemic, hypoxic or hypoglycemic CNS damage, neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, Parkinson's disease, epilepsy and stroke, as well as for use as an anticonvulsant, analgesic, antidepressant, anxiolytic and antipsychotic agent. A representative compound from a series of quinolinic sulfide derivatives, wherein the following are also included:



Compound	R1	R2	Formula
269006	H	3-Me-Ph	$C_{16}H_{12}ClNO_2S$
269007	H	3-F-Ph	[illegible]
269008	Cl	4-MeO-Ph	$C_{16}H_{11}Cl_2NO_3S$
269009	Cl	2-Br-Ph	$C_{15}H_8BrCl_2NO_2S$
269010	H	2-benzothiazolyl	[illegible]
269011	Cl	3-COOH-2-Pyr	[illegible]
269012	Cl	1,2,4-triazol-3-yl	[illegible]
269013	H	4-(PhCH2CONH)-Ph	[illegible]
269014	Cl	4-[...CONH]-Ph	[illegible]
269015	Cl	4-[4-Cl-PhCH2NH]-Ph	[illegible]

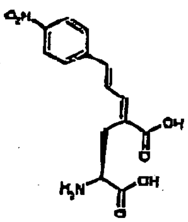
SOURCE – Korea Res. Inst. Chem. Technol., Taejon (KR).

REFERENCES

1. Park, N.S. et al. (Korea Res. Inst. Chem. Technol.) *Quinolinic sulfide derivs. acting as NMDA receptor antagonists and process for preparation thereof*. EP 869122, JP 98310578.

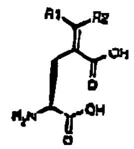
269083

(2S,E,E)-2-Amino-4-(4-nitrocinnamylidene)glutaric acid



C14 H14 N2 O6; Mol wt: 306.2728

ACTION – Neuroprotective agent, an ionotropic glutamate receptor agonist with selectivity for the GluR5 subtype (K_i < 1000 μM). Potentially useful for the treatment of neurodegenerative disorders such as stroke, cerebral ischemia, head and spinal cord trauma, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, AIDS-related dementia and Huntington's chorea, and also as an antipsychotic, anticonvulsant, analgesic, antiemetic, anxiolytic and antidepressant. Other specifically claimed glutamic acid derivatives include the following:



Compound	R1	R2	Formula
269084	4-N(Me)2-PhCH=CH	H	[illegible]
269085	CH=CHPh	H	[illegible]
269086	Bu	H	[illegible]
269087	Me	Me	[illegible]
269088	-(CH2)5-		[illegible]
269089	4-Cl-Ph	H	[illegible]
269090	-(CH2)6-		$C_{12}H_{12}ClNO_4$
269091	cyclopentyl	H	$C_{11}H_{19}NO_4$
269092	-(CH2)4-		$C_{11}H_{17}NO_4$
			$C_{10}H_{15}NO_4$

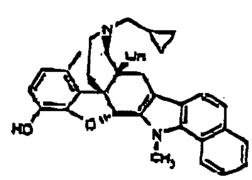
SOURCE – Lilly.

REFERENCES

1. Pedregal Tercero, C. and Rubio Esteban, A. (Lilly SA) *Glutamic acid derivs. and pharmaceutical compns. for the treatment of central nervous system disorders*. EP 862430, JP 98278342.

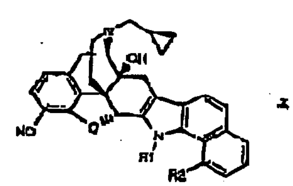
269145

17-(Cyclopropylmethyl) 4,5α-epoxy-3,14β-dihydroxy-1'-methyl-6,7-didehydro-1'H-benzo[6',7']indolo-[2',3':6,7]morphinan methanesulfonate



C31 H30 N2 O3 . C H4 O3 S; Mol wt: 574.6948

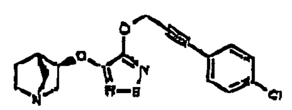
ACTION – Neuroprotective and cerebral antiischemic agent shown to exhibit potent protective effects against glutamate toxicity in cultured rat neurons (ED_{50} = 0.026 μM). It also reduced infarct volume in a rat model of middle cerebral artery occlusion–reperfusion injury (85% at 3 mg/kg i.p.). Other representative compounds within this series of indolomorphinane derivatives include the following:



Compound	R1	R2	X	Formula
269146	H	H	HCl	[illegible]
269147	H	Cl	MeSO3H	[illegible]
269148	CH2Ph	H	MeSO3H	[illegible]

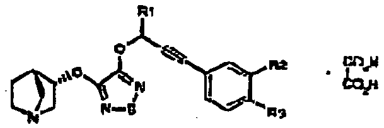
257732

(+)-exo-3-(1-Azabicycl [2.2.1]hept-3-yloxy)-4-[3 (4-chlorophenyl)-2-propynyloxy]-1,2,5-thiadiazole

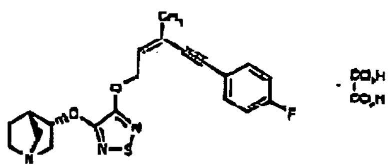


C17-H16-Cl-N3 O2 S; Mol wt: 361.85

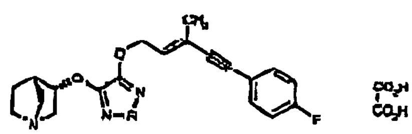
ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other specifically claimed heterocyclic compounds include the following:



Compound	R1	R2	R3	Formula
258610	Me	OMe	H	$C_{17}H_{21}N_3O_3S.C_2H_2O_4$
258611	H	H	Cl	$C_{17}H_{16}ClN_3O_2S.C_2H_2O_4$
258612	Et	OMe	H	$C_{20}H_{23}N_3O_3S.C_2H_2O_4$
258613	i-Pr	OMe	H	$C_{21}H_{25}N_3O_3S.C_2H_2O_4$
258614	H	CF3	H	$C_{18}H_{16}F_3N_3O_2S.C_2H_2O_4$
258643	H	H	F	$C_{17}H_{16}FN_3O_2S.C_2H_2O_4$
259764	H	F	H	$C_{17}H_{16}FN_3O_2S.C_2H_2O_4$



258616: C20-H20-F-N3-O2-S.C2-H2-O4



259763: C20-H20-F-N3-O2-S.C2-H2-O4

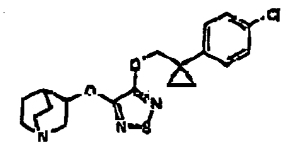
SOURCE – Lilly.

REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) Heterocyclic cpds. WO 9740043.

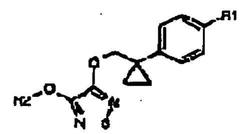
257733

(±)-3-[1-(4-Chlorophenyl)cyclopropylmethoxy]-4-(3-quinuclidinyloxy)-1,2,5-thiadiazole



C19-H22-Cl-N3-O2-S; Mol wt: 391.91

ACTION – Cognition-enhancing agent, a muscarinic cholinergic compound also useful for the treatment of glaucoma, psychosis and gastrointestinal motility disorders. Other exemplified heterocyclic compounds include the following:



Compound	R1	R2	Formula
258635	F	endo-(5R,6R)-1-azabicyclo[3.2.1]oct-6-yl	[illegible]
258636	Cl	2-azabicyclo[2.2.1]hept-6-yl	$C_{18}H_{20}ClN_3O_2S$
258637	Cl	3(R)-Pip	$C_{17}H_{20}ClN_3O_2S$

SOURCE – Lilly.

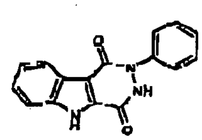
REFERENCES

1. Merritt, L. et al. (Eli Lilly & Co.) Heterocyclic cpds. WO 9740044.

TREATMENT OF CEREBROVASCULAR DISEASES

257448

2-Phenyl-2,3,4,5-tetrahydro-1*H*-pyridazino[4,5-*b*]indole-1,4-dione



C16-H11-N3-O2; Mol wt: 277.28

ACTION – Selective and noncompetitive NMDA receptor antagonist that preferentially binds to the strychnine-insensitive glycine binding site associated with the NMDA receptor complex. Compound blocked the response to NMDA in rat cortex slices (K_b < 150 μM) and displaced [^{3}H]-L-689560 binding to the strychnine-insensitive site in rat forebrain membranes (IC_{50} < 50 μM). Potentially useful in the treatment or prevention of neurodegenerative disorders such as stroke, cerebral ischemia, epilepsy, Huntington's chorea, Alzheimer's disease, Parkinson's disease and anoxia.

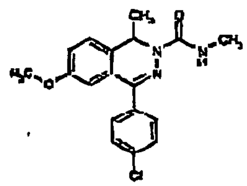
SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Lakshmanhotty, V. and MacLeod, A.M. (Merck Sharp & Dohme, Ltd.) *Pyridazinamide derivs.* US [illegible].

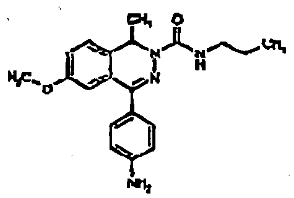
257717

4-(4-Chlorophenyl)-6-methoxy-*N*,1-dimethyl-1,2-dihydrophthalazine-2-carboxamide



C18-H18-Cl-N3-O2; Mol wt: 343.81

ACTION – A noncompetitive AMPA receptor antagonist potentially useful in the treatment of neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, hypoxia, anoxia, hypoglycemia, stroke, epilepsy, schizophrenia and migraine. Another specifically claimed compound from this series of phthalazine derivatives is:



258754: C20-H24-N4-O2

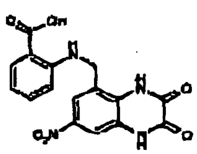
SOURCE – Schering AG.

REFERENCES

1. Orlow, E. et al. (Schering AG) *Phthalazine derivs., their preparation and their use as drugs.* DE [illegible], WO [illegible].

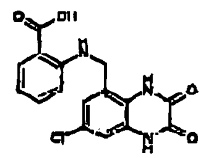
258857

2-(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethylamino)benzoic acid



C16 H12-N4-O6; Mol wt: 356.29

ACTION – Dual glycine-site NMDA and AMPA receptor antagonist with respective IC_{50} values in binding assays of 0.05 ± 0.02 and 0.05 ± 0.01 μM. Potentially useful as a neuroprotective agent or for the treatment of epilepsy. Another compound from this series of 5-arylaminomethylquinoxaline-2,3-diones with selectivity for the glycine binding site of the NMDA receptor is:



258858: C16-H12-Cl-N3-O4

SOURCE – Novartis.

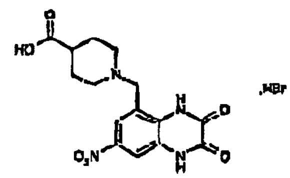
REFERENCES

1. Acklin, P. et al. (Novartis AG) *Novel 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalinyl derivs.* WO [illegible].

2. Auberson, Y.P. et al. *5-Aminomethylquinoxaline-2,3-diones. Part II: N-Aryl derivatives as novel NMDA/glycine and AMPA antagonists.* Bioorg Med Chem Lett 1998, 8(1): 71.

258859

1-(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethyl)piperidine-4-carboxylic acid hydrobromide



C15-H16-N4-O6.HBr; Mol wt: 429.23

ACTION – Potent and selective AMPA receptor antagonist, as shown in binding assays (IC_{50} = 0.07 μM), with good water solubility. It exhibited significantly weaker activity at the glycine binding site of the NMDA receptor (IC_{50} = 3.9 μM). Compound provided protection against electroshock-induced convulsions in mice with moderate potency (ED_{50} = 44 mg/kg i.p.), but ataxia was observed at doses near the ED_{50}.

SOURCE – Novartis.

REFERENCES

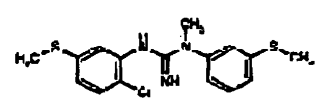
1. Acklin, P. et al. (Novartis AG) *Novel 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalinyl derivs.* WO [illegible].

2. Auberson, Y.P. et al. *5-Aminomethylquinoxaline-2,3-diones. Part I: A novel class of AMPA receptor antagonists.* Bioorg Med Chem Lett 1998, 8(1): 65.

CNS-5161

228550

N^2-[2-Chloro-5-(methylsulfanyl)phenyl]-N^1-methyl-N^1-[3-(methylsulfanyl)phenyl]guanidine



C16-H18-Cl-N3-S2; Mol wt: 351.91

Hydrochloride salt, m.p. 203-4 °C.

HEK4BP

239817

Polypeptide that binds to the HEK4 receptor

HEK4-binding protein

ACTION – HEK4 receptor-binding protein that binds to one or more of the EPH-like receptors, particularly the HEK4 receptor. The polypeptide is useful for modulating the growth and/or differentiation of a variety of tissues, for example, liver, kidney, lung, skin or neural tissue, and may be useful in the treatment of CNS disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and spinal cord injury, and for the regeneration of damaged tissues. Antagonists of this polypeptide may be useful in the treatment of cancer.

SOURCE – Amgen.

REFERENCES

1. Bartley, T.D. and Fox, G.M. (Amgen, Inc.) *Ligands for EPH-like receptors.* WO 9823000.

YM-49635

240641

4,4,17,17-Tetramethyl-1,20-bis(*N*-methyltridecanamido)-8,13-diaza-4,17-diazoniaeicosane dichloride

C44-H94-Cl2-N6-O2 ; Mol wt 810.17

ACTION – Cognition-enhancing agent extracted from the sponge *Erylus* sp., with high affinity for the N-type calcium channel (IC_{50} = 5.8 µM against [^{125}I]-ω-conotoxin binding). Another tetraazaeicosane compound from this source is:

YM-49636 [241105]; C22-H54-Cl2-N6

SOURCE – Yamanouchi.

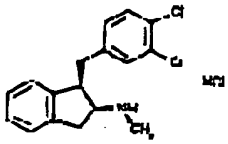
REFERENCES

1. Fusetya, N. et al. (Yamanouchi Pharm. Co., Ltd.) *Tetraazaeicosane cpds.* JP 9517744.

TREATMENT OF CEREBROVASCULAR DISEASES

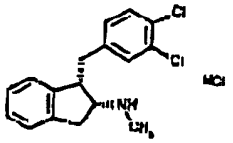
239793

(–)-*cis*-*N*-[1-(3,4-Dichlorobenzyl)indan-2-yl]-*N*-methylamine hydrochloride



C17-H17-Cl2-N HCl ; Mol wt: 342.69

ACTION – Agent for the treatment of ischemic stroke, a single enantiomer of a known neuronal calcium antagonist proven to induce 99% inhibition of plateau Ca^{2+} current in superior cervical ganglion neurons (*N*-type calcium current) at a concentration of 5 µM. It is reported to significantly attenuate histological damage in cerebral ischemic models using gerbils and mice. The other single enantiomer is:



240451; C17-H17-Cl2-N.HCl (+) *cis*-isomer

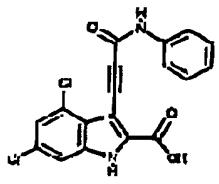
SOURCE – SmithKline Beecham.

REFERENCES

1. Crist, B.S. and Kerling, J.D. (SmithKline Beecham plc) *Enantiomers of 1-(3,4-dichlorobenzyl)-2-methylaminoindane.* WO 9521141.

240624

4,6-Dichloro-3-(*N*-phenylcarbamoylethynyl)-1*H*-indole-2-carboxylic acid



C18-H10-Cl2-N2-O3 ; Mol wt: 373.19

ACTION – An NMDA antagonist acting at the strychnine-insensitive glycine binding site and structurally related to GV-150526, for use in the treatment of CNS disorders such as stroke, Huntington's disease, Alzheimer's disease and neurotrauma. Its affinity (pK_i = 7.7) is inferior to that of GV-150526 (pK_i = 8.5), but it displayed good *in vivo* activity in mice against NMDA-induced convulsions (ED_{50} = 0.2 mg/kg i.v.; ED_{50} GV-150526 = 0.06 mg/kg i.v.).

SOURCE – Glaxo Wellcome.

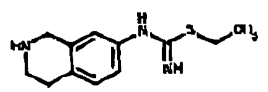
REFERENCES

1. Cugola, A. and Gaviraghi, G. (Glaxo SpA) *Indole antagonists of excitatory amino acids.* GB 1998143, CH 685030, EP 568136, FR 2690910, GB 2266091, JP 94048027, US 5375014, US 4074648, US 5374649, WO 9321153.

2. Di Fabio, R. et al. *3-Alkyl-2-carboxyindoles as a novel class of antagonists acting at the strychnine-insensitive glycine binding site.* 14th Int Symp Med Chem (Sept 8-12, Maastricht) 1996, Abst P-8.17.

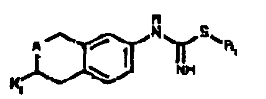
240961

N-(1,2,3,4-Tetrahydroisoquinolin-7-yl)carbamimidothioic acid ethyl ester



C12-H17-N3-S ; Mol wt: 235.35

ACTION – Agent for the treatment of neurodegenerative disorders that displays neuronal nitric oxide synthase (NOS)-inhibitory activity (IC_{50} < 10 μM); compound displayed a good level of selectivity as it inhibited inducible and endothelial forms of the enzyme at concentrations at least 10 times higher. Other specifically claimed bicyclic isothiourea derivatives include the following:



242637; C20-H24-Cl-N3-S: R1= Et, R2= 3-Cl-PhCH2N(Me), A= bond
242638; C14-H20-N2-S: R1= Et, R2= Me, A= CH2
242639; C13-H18-N2-S: R1=R2= Me, A= CH2

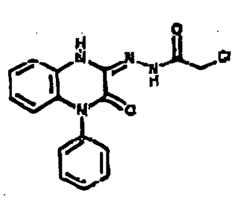
SOURCE – Astra.

REFERENCES

1. MacDonald, J.E. (Astra AB) *Bicyclic isothiourea derivs. useful in therapy.* WO9824638.

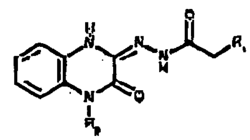
240999

2-Chloro-*N*'-(3-oxo-4-phenyl-1,2,3,4-tetrahydroquinoxalin-2-ylidene)acetohydrazide



C16-H13-Cl-N4-O2 ; Mol wt: 328.76

ACTION – Agent for the treatment of neurodegenerative disorders, an inhibitor of both calpain I and calpain II (IC_{50} = 0.384 and 0.590 μM, respectively, using enzyme from human erythrocytes), with negligible inhibitory activity against other proteases such as cathepsin B, trypsin and thermolysin (IC_{50} > 200 μM). Compound proved effective in protecting against the toxic effects of AMPA to Purkinje cells in cerebellar slices, and against the effects of oxygen/glucose deprivation in fetal rat cortical cell cultures. Other specifically claimed α-substituted hydrazides include the following:



241510; C11-H11-Cl-N4-O2: R1= Cl, R2= Me
241511; C16-H13-Br-N4-O2: R1= Br, R2= Ph
241512; C16-H12-Cl2-N4-O2: R1= Cl, R2= 4-Cl-Ph

SOURCE – Warner-Lambert.

REFERENCES

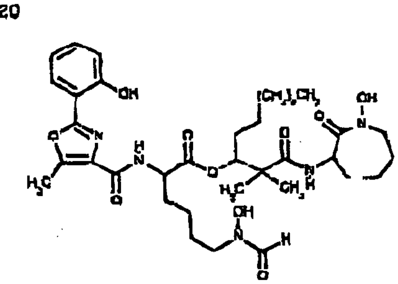
1. Wang, K.K.-W. and Yuen, P.-W. (Warner-Lambert Co.) *α-Substd. hydrazides having calpain inhibitory activity.* WO 9825403.

FORMOBACTIN

240625

6-(*N*-Hydroxyformamido)-2-[2-(2-hydroxyphenyl)-5-methyloxazol-4-ylcarboxamido]hexanoic acid 1-[1-[*N*-(1-hydroxy-2-oxoperhydroazepin-3-yl)carbamoyl]-1-methylethyl]decyl ester

ND-20



C38-H57-N5-O10 ; Mol wt: 743.90

White powder, m.p. 68-72 °C (decomp.), $[\alpha]_D^{25}$ –8.6° (c 1.0, MeOH).

ACTION – Neuroprotective agent and lipid peroxidation inhibitor isolated from the mycelium of *Nocardia* sp. ND20. It inhibited free radical-induced lipid peroxidation in rat brain homogenates with an IC_{50} of 0.66 μM, being more potent than butylated hydroxytoluene (BHT; IC_{50} = 1.80 μM). In addition, it protected against L-glutamate toxicity in neuronal hybridoma N18-RE-105 cells (EC_{50} = 0.017 μM) and inhibited buthionine sulfoximine-induced apoptosis in these cells (EC_{50} = 0.072 μM)